ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.015

EXPEDITED REVIEWS

Primary Results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT)

A Multicenter Study of B-Type Natriuretic Peptide Levels, Emergency Department Decision Making, and Outcomes in Patients Presenting With Shortness of Breath

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OBJECTIVES The purpose of this study was to examine the relationships among B-type natriuretic peptide (BNP) levels within the diagnostic range, perceived congestive heart failure (CHF) severity, clinical decision making, and outcomes of the CHF patients presenting to emergency department (ED).

BACKGROUND Since BNP correlates with the presence of CHF, disease severity, and prognosis, we hypothesized that BNP levels in the diagnostic range offer value independent of physician decision making with regard to critical outcomes in emergency medicine.

METHODS The Rapid Emergency Department Heart failure Outpatient Trial (REDHOT) study was a 10-center trial in which patients seen in the ED with shortness of breath were consented to have BNP levels drawn on arrival. Entrance criteria included a BNP level >100 pg/ml. Physicians were blinded to the actual BNP level and subsequent BNP measurements. Patients were followed up for 90 days after discharge.

RESULTS Of the 464 patients, 90% were hospitalized. Two-thirds of patients were perceived to be New York Heart Association (NYHA) functional class III or IV. The BNP levels did not differ significantly between patients who were discharged home from the ED and those admitted (976 vs. 766, p = 0.6). Using logistic regression analysis, an ED doctor's intention to admit or discharge a patient had no influence on 90-day outcomes, while the BNP level was a strong predictor of 90-day outcome. Of admitted patients, 11% had BNP levels <200 pg/ml (66% of which were perceived NYHA functional class III or IV). The 90-day combined event rate (CHF visits or admissions and mortality) in the group of patients admitted with BNP <200 pg/ml and >200 pg/ml was 9% and 29%, respectively (p = 0.006).

CONCLUSIONS In patients presenting to the ED with heart failure, there is a disconnect between the perceived severity of CHF by ED physicians and severity as determined by BNP levels. The BNP levels can predict future outcomes and thus may aid physicians in making triage decisions about whether to admit or discharge patients. Emerging clinical data will help further refine biomarker-guided outpatient therapeutic and monitoring strategies involving BNP. (J Am Coll Cardiol 2004;44: 1328–33) © 2004 by the American College of Cardiology Foundation

Congestive heart failure (CHF) is a major and increasing cause of death and disability worldwide. In the U.S. alone, the prevalence of heart failure is 4.6 million, with an incidence rate of 550,000 new cases a year and approximately 957,000 hospitalizations annually (1). The economic cost of CHF is estimated at $56 billion a year, 70% of which is due to hospitalization (2). One-third of patients with known CHF are admitted annually to the hospital, most of these through the emergency department (ED) (3).

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Between 75% to 90% of all patients presenting to the ED with presumed CHF are admitted to the hospital, leading to exorbitant costs and resource utilization (4). This high percentage of admissions is in part due to the absence of reliable clinical or laboratory criteria that could aid in the disposition decision. Although signs and symptoms of CHF

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Manuscript received February 12, 2004; revised manuscript received June 1, 2004, accepted June 8, 2004.

Abbreviations and Acronyms

BNP	= B-type natriuretic peptide
CHF	= congestive heart failure
ED	= emergency department
NYHA	= New York Heart Association
REDHOT	= Rapid Emergency Department Heart failure Outpatient Trial
SOB	= shortness of breath

may aid in the initial diagnosis of CHF, there is a poor relationship between symptoms of CHF and both the severity of cardiac dysfunction and prognosis.

B-type natriuretic peptide (BNP) levels have been used to successfully aid in the diagnosis of CHF in patients presenting with dyspnea (5–10). Because BNP levels correlate with both disease severity and prognosis (11–16) they should be of value in assisting in the appropriate management and eventual disposition of CHF patients in the ED. The purpose of the study was to illustrate the relationships among BNP levels within the diagnostic range, clinical decision making, and outcomes. If the magnitude of BNP elevation above the traditional diagnostic threshold of 100 is prognostic, then it may be useful in deciding ultimate admission or discharge from the ED and other clinical judgments.

METHODS

Study population. The study was approved by the institutional review boards of participating REDHOT study centers. The subject sample consists of a total of 464 patients at 10 sites who were enrolled from June 12, 2001 to February 3, 2003. Patients over the age of 18 years presenting to the ED with CHF and who received treatment in the ED or hospital admission for CHF were included. Current myocardial infarction (MI) or acute coronary syndrome with ST-segment deviation of ≥1 mm, renal failure requiring dialysis, or patients with a baseline BNP concentration of ≤100 pg/ml were excluded. Once written consent was obtained, a blood sample was collected for purposes of measuring the patient's BNP concentration. The study coordinator ran these assays on-site at the point of care. Physicians were told only whether or not the patient met study criteria (BNP level >100 pg/ml).

After their initial clinical evaluation, physicians were asked to rate the severity of disease (New York Heart Association [NYHA] functional class I to IV) and whether or not they believed the patient would ultimately be admitted to the hospital (initial disposition). The research assistant collected other data including elements from the present and past history, the physical examination, reports of other blood tests, interpretations of chest X-rays, and interpretations of other diagnostic tests. Blood for BNP levels was drawn every 3 h while in the ED and at the time patients were either admitted to the hospital or discharged home. These data are not published because of marked attrition rates, as we lost 75% of our patients by 3 h owing to the clinical decisions and subsequent patient disposition. Patient follow-up occurred at 30 and 90 days following either discharge from the ED or the hospital. Follow-up occurred via telephone interview, chart review, or by mail. The events recorded were CHF-related visits (ED and hospital admissions), and all-cause mortality.

Measurement of BNP plasma levels. During initial evaluations, a blood sample was collected into tubes containing potassium ethylene diamine tetra-acetic acid. The BNP was measured using the Triage B-Type Natriuretic Peptide test (Biosite Inc., San Diego, California) (16). The Triage BNP test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma specimens. The precision, analytical sensitivity, and stability characteristics of the system have been previously described (5,12,17,18). The BNP values were determined on-site utilizing the point-of-care method with either whole blood or plasma samples.

Statistical analysis. Continuous variables were summarized with medians and quartiles (25th and 75th percentiles) while frequency counts were given for nominal variables. A chi-square test was used to compare disposition decisions to outcomes. The BNP levels were compared between disposition and outcome groups using Mann-Whitney *U* tests and among groups based on perceived severity (NYHA) using a Kruskal-Wallis test. Logistic regression was used to evaluate the power of BNP in combination with perceived severity (NYHA functional class) and ED disposition for predicting outcomes. A receiver-operating characteristic (ROC) curve was also calculated for prediction of death from BNP levels. Admitted patients were divided into two groups based on BNP levels above and below 200 pg/ml to study differences in outcome rates using chi-square tests. This cutoff value for 200 pg/ml BNP was chosen retrospectively based on statistical analyses and clinical outcomes. This number had to be higher than the diagnostic value of 100 pg/ml but low enough to have high negative predictive value and still retain a significant number of patients to actually make a difference. Study power estimates were computed assuming that non-parametric tests are 95% as powerful as their parametric counterparts (19). A medium effect size estimate of 0.5 standard deviation units was selected (20). Using an alpha criterion of 0.05 and the sample sizes for the comparisons of BNP levels in various patients groups—discharged or admitted patients, dead or alive patients at 30 days, and dead or alive patients at 30 days—yielded power estimates of 0.84, 0.45, and 0.78, respectively.

RESULTS

The study cohort consisted of 464 patients (Table 1) including 46.1% females. The median age was 64 years, and there was a preponderance of African Americans (63.4%). The majority of patients presented to the ED with symp-

JACC Vol. 44, No. 6, 2004
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Table 1. Patient Characteristics

Variable (N)	Percentage or Median (Quartiles)
Male (%) (464)	53.9
Race (464)	
Caucasian (%)	32.5
African-American (%)	63.4
Hispanic (%)	3.7
Asian (%)	0.4
Age (yrs) (464)	64 (51–76)
Height (inches) (451)	67 (65–70)
Weight (lbs) (460)	190 (154–240)
Systolic BP (mm Hg) (462)	141 (121–166)
Diastolic BP (mm Hg) (462)	81 (67–97)
Heart rate (462) (beats/min)	92 (77–106)
Exam variables	
PND (400)	59.0
Elevated JVD >6 cm (413)	42.6
Orthopnea (439)	78.4
Pulmonary rales (456)	74.8
Wheezing (453)	27.6
Ascites (438)	9.6
Chest pain (460)	30.7
Ankle/peripheral edema (460)	75.0
S3 gallop (445)	19.6
Murmurs (445)	22.0
Diffuse and lateral PMI (445)	12.1
X-ray variables	
Increased heart size (458)	47.8
Interstitial edema (458)	50.7
Intra-alveolar edema (458)	19.8
Pleural effusion (458)	22.5
Laboratory tests	
Serum creatinine (mg/dl) (451)	1.2 (0.95–1.7)
Oxygen saturation (%) (437)	96 (93–98)
Max troponin I (ng/ml) (409)	0.3 (0.1–0.3)*
Max CK-MB (ng/ml) (305)	2.6 (1.6–4.9)
History variables	
Hypertension (456)	77.2
Diabetes (456)	40.6
Smoke >100 cig/yr (440)	39.5
Alcohol use (433)	23.1
COPD (442)	21.7
Asthma (450)	16.9
Myocardial infarction (437)	33.4
Angina (437)	33.4
Valve disease (406)	23.6
Atrial fibrillation (426)	25.4
Cardiac surgery (447)	29.1
CHF (446)	76.5
CHF-related hospital visits in last 3 months (407)	42.0
CHF-related hospital admissions in last 3 months (405)	37.5
Perceived NHYA functional class	
I	3.0
II	29.
III	45.0
IV	22.6

*Owning the low discriminatory power of the old troponin I laboratory machine especially in the lower ranges many patients had a level of 0.3. In actuality, only 11% were above normal cutoff levels used at that time (0.6 ng/ml).

BP = blood pressure; CHF = congestive heart failure; CK-MB = creatine kinase-MB fraction; COPD = chronic obstructive pulmonary disease; JVD = jugular venous disease; NYHA = New York Heart Association; PMI = point of maximal intensity; PND = paroxysmal nocturnal dyspnea.

toms suggestive of CHF, such as paroxysmal nocturnal dyspnea (59%) and orthopnea (78.4%). Concomitant chest pain was reported in 30.7% of the cases. A history of CHF was noted in 76.5% of cases and 42.0% had CHF-related hospital visits in the previous three months. At the time of initial assessment in the ED, 67.8% of patients were perceived to be either NYHA functional class III or IV (Table 1).

The overall hospitalization rate was 90.3%, even though physicians only intended to admit 68.3% upon initial evaluation (Table 2). There were 15 patients (3.2%) who died by the 30-day point and 36 patients (7.8%) expired by the 90-day point. Events included all-cause mortality and re-admission or ED visits for cardiac symptoms. Discharged patients were more likely to experience an event (19 of 45 or 42.2%) than were admitted patients (110 of 425 or 25.9%) by the 90-day follow-up ($p = 0.02$).

Figure 1 shows the median BNP levels in patients as a function of perceived NYHA functional classification. The BNP levels did not differ significantly among the perceived NYHA functional classifications ($p = 0.124$). This "disconnect" between the perceived severity and BNP level is further corroborated by Figure 2A, which shows that the BNP levels in patients who were discharged home were not significantly different from those who were admitted to the hospital (976 vs. 767 pg/ml, $p = 0.6$). Figure 2 also shows BNP levels in relation to subsequent 30-day (Fig. 2B) and 90-day (Fig. 2C) mortality. The median BNP levels were significantly higher in the deceased patient group as compared to surviving patient group, using both 30-day and 90-day follow-up periods (2,096 pg/ml vs. 764 pg/ml, $p < 0.001$, and 1,224 pg/ml vs. 727 pg/ml, $p = 0.001$, respectively).

Table 3 shows logistic regression analyses predicting 90 day outcomes from BNP values along with ED disposition. Although the BNP level was a strong predictor of mortality and events (mortality, cardiac readmissions, and cardiac visits) perceived severity (NYHA functional class ratings) and ED disposition (intention and actual) did not contribute to the prediction of 90-day outcomes. Figure 3 shows the ROC curve for BNP in predicting 90-day all-cause mortality. The area under the ROC curve was 0.670 ± 0.045 ($p < 0.001$).

Because most patients were actually admitted, groups were formed to illustrate the outcomes for admitted patients with relatively low BNP levels. The difference between admitted patients with initial BNP levels above and below 200 pg/ml was examined in terms of ultimate outcome (Table 4). Among the admitted patients, 11% (43 patients) had BNP levels <200 pg/ml; 66% of these patients were perceived to be NYHA functional classification III or IV. The 90-day combined event rate (CHF visits or admissions or all cause mortality) in the group of patients admitted with BNP <200 pg/ml was 9% compared to those admitted with BNP >200 pg/ml, which was 29% ($p = 0.006$). The groups

Table 2. Initial Intent, Final Disposition, and Follow-Up Events

Intended Disposition	Actual Disposition	30-Day Outcomes (7 Patients Lost to Follow-Up)		90-Day Outcomes (12 Patients Lost to Follow-Up)	
		Death	Death or Cardiac Visit	Death	Death or Cardiac Visit
Discharge (n = 147)	Discharged (n = 39)	0 (0.0%)	10 (25.6%)	2 (5.1%)	17 (43.6%)
	Admitted (n = 108)	3 (2.8%)	24 (22.2%)	9 (8.3%)	33 (30.6%)
Admit (n = 317)	Discharged (n = 6)	0 (0.0%)	1 (16.7%)	1 (16.7%)	2 (33.3%)
	Admitted (n = 311)	12 (3.8%)	55 (17.4%)	24 (7.6%)	77 (24.3%)

did not differ significantly in terms of mortality alone (p = 0.142).

DISCUSSION

The rising prevalence of CHF in the U.S. is not surprising. People are surviving MIs even with poor ventricular function, and newer medications allow patients with established CHF to live longer and more productive lives. What is surprising is that up to 90% of CHF patients seen in the EDs are admitted to the hospital (4). The resource utilization for this group of patients is about 70% of the total costs of heart failure (2). Comparatively, only about 37% to 60% of patients seen with chest pain are admitted to the hospital (21). This is because there are excellent tools available to help triage and to prognosticate (e.g., electrocardiograms and troponins) in this group of patients, yet patients with heart failure are usually admitted based on subjective evaluation of the patient's symptoms.

It is surprising that BNP levels have thus far not been used to any large degree to help guide treatment and disposition decisions in patients who present to the ED with CHF. The Breathing Not Properly multinational study clearly demonstrated that BNP levels could aid a physician in making the diagnosis of heart failure, yet a recent editorial suggested that a competent physician does not need a BNP level to evaluate and treat patients with heart failure (22). The present study, however, shows that perception of severity of CHF among ED physicians does not in fact correlate well with BNP levels; patients sent home from the ED actually showed a trend toward higher BNP levels than did those admitted, yet BNP levels were much stronger predictors of subsequent outcome. This gives credence to the contention that a "disconnect" exists between the perceived severity of illness and BNP values, a notion that should help decision-making. The present study demonstrates that most admitted patients had perceived NYHA functional class III or IV; however, if the BNP level was <200 pg/ml, the overall prognosis was excellent. Had

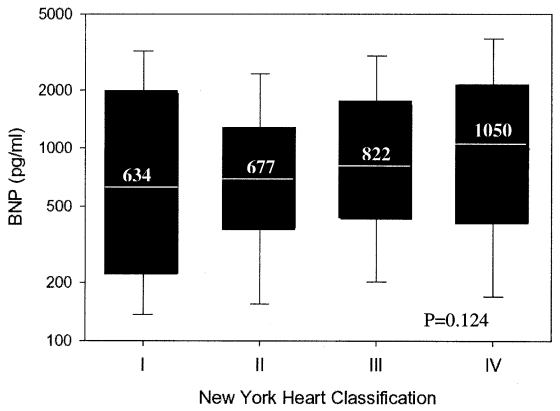

Figure 1. Box and whisker plots of B-type natriuretic peptide (BNP) levels by perceived New York Heart Association functional classification at time of presentation at the emergency department. Medians are presented. **Boxes** illustrate upper and lower quartiles, and **whiskers** illustrate the 10th and 90th percentiles.

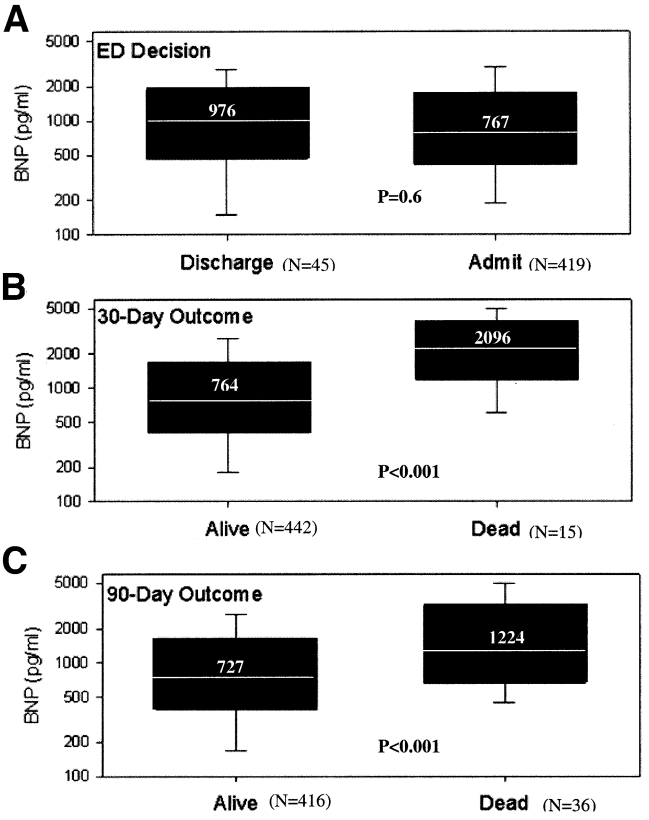

Figure 2. The B-type natriuretic peptide (BNP) distributions for various patient groups. **(A)** The BNP levels versus the decision to discharge or admit the patient. **(B)** The BNP levels based on whether patients were alive or dead at 30 days. **(C)** The BNP levels based on whether patients were alive or dead at 90 days Medians are presented. **Boxes** illustrate upper and lower quartiles, and **whiskers** illustrate the 10th and 90th percentiles. ED = emergency department

Table 3. Logistic Regression

Logistic Regression to Predict 90-Day Mortality from BNP, NYHA Functional Class, and Disposition Variables

Variable	B	S.E.	p Value	Exp(B)*
Log BNP	1.537	0.42	0.001	4.531
NYHA functional class	0.140	0.228	0.648	1.110
Initial intent	−0.057	0.410	0.889	0.944
Actual disposition	0.231	0.681	0.735	1.260

Logistic Regression to Predict 90-Day Events (Mortality or Cardiac-Related Admission or ED Visit) from BNP, NYHA Functional Class, and Disposition Variables

Variable	B	S.E.	p Value	Exp(B)*
Log BNP	0.708	0.254	0.005	2.030
NYHA functional class	−0.091	0.137	0.507	0.913
Initial intent	−0.368	0.243	0.130	0.692
Actual disposition	−0.433	0.360	0.229	0.649

*Exp(b) is the odds-ratio for the binary variables of intent and disposition, but this is not the case for log B-type natriuretic peptide (BNP) or New York Heart Association (NYHA) functional class.

baseline BNP levels been known, the absolute magnitude of change of BNP levels might have been even a better predictor of outcome than the absolute BNP level. Further work should be done in this area.

Toward triaging patients with CHF based on BNP levels. The B-type natriuretic peptide for Acute Shortness of breath EvaLuation (BASEL) study (23) randomized 425 patients presenting with dyspnea into BNP availability versus no BNP availability. The group that had BNP available to them utilized less time in the emergency area making the diagnosis, had fewer admitted patients to the hospital, and in those patients admitted to the hospital had less utilization of costly intensive care unit beds. The fact that there was a 26% reduction in total costs when BNP was available suggests BNP's utility in decision making.

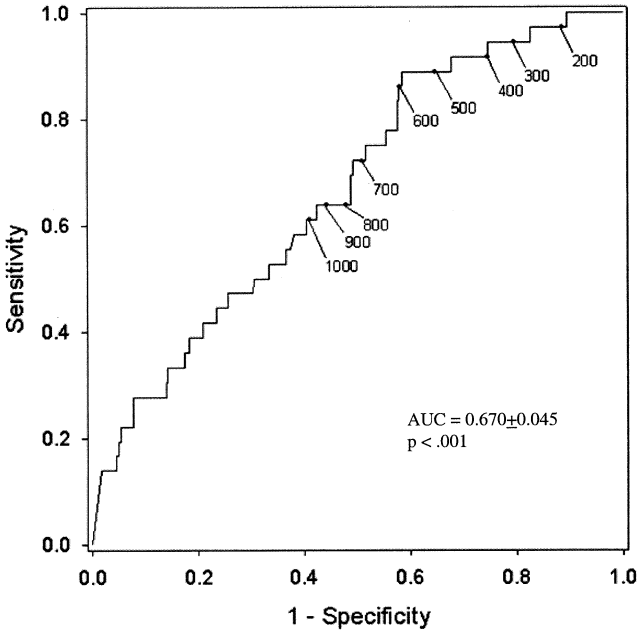

Figure 3. Receiver-operating-characteristic curve for B-type natriuretic peptide in predicting 90-day mortality. AUC = area under the curve.

It is not surprising that BNP levels are predictive of prognosis. Cheng et al. (12) followed the course of 72 patients admitted with decompensated CHF with daily BNP levels and their relationship to 30-day readmission rates or death. Patients whose discharge BNP levels fell <430 pg/ml had a reasonable likelihood of not being readmitted within the following 30 days. The data were supported by a recent study by Bettencourt et al. (13) who found that failure of BNP levels to decline during the hospitalization period is a predictor of death/rehospitalization, and that discharge levels <250 pg/ml predicted event-free survival. Recently, Harrison et al. (11) showed that BNP levels measured in 325 patients presenting with dyspnea to the ED were highly predictive of cardiac events (cardiac death, ED visit, or admission for a cardiac cause) over the ensuing six months. Patients with BNP levels >480 pg/ml had a 51% six-month cumulative probability of a CHF event. Alternatively, patients with BNP levels <230 pg/ml had an excellent prognosis, with only 2.5% incidence of death (cardiac and non-cardiac), hospital admissions (cardiac), and repeat ED visits for CHF.

The above studies along with the results of the present trial strongly suggest that BNP levels can be utilized to help make disposition and management decisions that will ultimately affect cost and outcomes. This is especially true in patients with low BNP levels, who may not always need to be admitted. For example, diagnosis-related group-127 accounts for 80% of all CHF admissions. With 680,106 hospital admissions in 2001, and with a 5.27-day average length of stay and average cost of $5,414.68 per patient, there is a total expenditure of $4.6 billion. Eleven percent of the patients in this study were admitted with BNP levels <200 pg/ml. If BNP levels could decrease hospital admissions by this percentage, there would be an estimated $500 million savings. Thus, small improvements in disposition decisions may have a large impact on health care economics. There is no way to know whether the decreased mortality seen in patient groups with BNP levels <200 pg/ml in this study who were admitted was due to treatment or because they had less severe disease to begin with, even though the latter is more likely owing to known correlation of BNP levels to left ventricular filling pressure, NYHA functional

Table 4. The Percentages of Various Outcomes for Admitted Patients Divided into Groups Based on a BNP Cut Point of 200 pg/ml

Admitted Patients	BNP <200 pg/ml (n = 43)	BNP >200 pg/ml (n = 364)	p Value
NYHA functional class III and IV	66%	70%	0.598
Combined event rate	9%	29%	0.006
Mortality	2%	9%	0.142

Combined events include cardiac-related admissions or visits, or all-cause mortality. BNP = B-type natriuretic peptide; NYHA = New York Heart Association.

classification, and severity of CHF. Thus, it is not possible to recommend discharging a patient solely on the basis of a BNP level <200 pg/ml; rather, each patient should be evaluated on a per case basis. However, patients with BNP levels <200 pg/ml had an excellent prognosis, even if CHF was judged as severe.

Further studies might demonstrate that treatment decisions could be based on changes in BNP levels with initial treatment. Having baseline "dry" BNP levels available might add to the value of BNP levels in guiding treatment decisions.

Study limitations. In this study, clinicians were blinded to BNP levels, so we were not able to prospectively assess the ability to improve patient disposition based on BNP levels. We cannot say what effect putting the patient in the hospital versus not hospitalizing the patient would have on ultimate outcomes. Finally, we could not truly control for treatment interventions that occurred over the 90-day follow-up period.

Conclusions. In patients presenting to the ED with shortness of breath (SOB), there is a large "disconnect" between the perceived severity of heart failure (as assessed by initial disposition and NYHA functional class) and the BNP level. Even in the setting where CHF severity is perceived as severe, a low BNP level portends a favorable prognosis. This study was not designed to assess whether patients with low BNP levels can be safely managed as an outpatient; rather, it simply states that a rapid point-of-care BNP test in the ED can lead not only to accurate diagnosis of CHF but also might assist in the assessment of disease severity and prognosis. The level of elevation of BNP appears to be a better reflection of 90-day outcomes than current disposition decisions and may be useful to stratify and triage patients. This might decrease prolonged stays in the ED, reduce unnecessary hospitalizations, decrease inappropriate discharges home, and overall lead to better patient care. Emerging clinical data will help further refine biomarker-guided outpatient therapeutic and monitoring strategies involving BNP.

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APPENDIX

For a list of the REDHOT study investigators, please see the September 15, 2004, issue of *JACC* at www.cardiosource.com/jacc.html.